REMARKS

Claims 1 – 3, 43 – 45 and 49 are pending in the application. Claims 3 – 42 and 46 – 48 have been cancelled. Claims 1 and 2 have been amended. No new claims have been added.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

Objections

Claim 2 has been objected to for minor errors. (Office Action, p.2). Applicants have corrected these errors and respectfully request that the foregoing rejection be withdrawn.

35 U.S.C. §112, first paragraph

Enablement

Claims 1 – 3, 43 – 45 and 49 were rejected under 35 U.S.C. §112, first paragraph. (Office Action, p.2). The Examiner argues that "the specification, while being enabling only for a targeted glycoconjugate comprising a specific bioactive agent as shown the specific anticancer agent listed at pages 14 – 15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP-galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase for detection assays, **does not** reasonably provide enablement for (1) any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a

modified UDP galactose acetyl group (UDP-GalNAc) compris(ing) a ketone group attached to the C2 position of the galactose ring" as claimed. Applicants respectfully disagree.

The Examiner argues that "(t)he claims encompass innumerous targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified UDP galactose acetyl group having a ketone attached to the C2 position of the galactose ring for use in any and all medical therapy." (Office Action, p.4). The Examiner argues that "(e)nablement is not commensurate in scope with how to use any unspecified targeted glycoconjugate comprising any bioactive agent and any targeting compound for the claimed targeted glycoconjugate." (Office Action, p.4). The Examiner argues that "(t)he specification discloses only labeling of CREB or bovine lens α-crystallin using recombinant O-Glc-NAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase…(and) the specification discloses only modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group attached at the C-2 position of the galactose ring using mutant Y289L galactose transferase…(and) other than the specific glycoconjugate comprising the specific bioactive agent mentioned above and the specific targeting compound mentioned above…the specification does not teach the use of targeted glycoconjugate comprising any bioactive agent linked to any targeting compound via modified UDP galactose acetyl group attached to the C2 position of the galactose ring for treating any disease, much less for preventing all diseases." (Office Action, p. 4 – 5).

The invention as claimed is a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

The claims recite that the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. The specification teaches that modification of the saccharide to include a functional group, such as a ketone group, aids in the attachment of the bioactive agent. The specification provides examples of such ketone attachments. For example, on page 10, the

specification teaches that "the modified saccharide (S) may include a ketone moiety which can be reacted with an amino group of a bioactive agent of interest so as to form a covalent bond between the two."

Applicants point out again that the specification teaches that the C2 position is favorable over other positions on the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C2 positions. Applicants teach appending the ketone functionality particularly at the C-2 position of the galactose ring. At page 48 of the specification, Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that "the ketone functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 positions, including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ian et al., 2001; Wong et al., 1995) (and)... 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3-, 4, and 6-deoxy-Gal were transferred at reduced rates." (p. 48, emphasis added).

The specification teaches at page 11 beginning at line 5, various methods that can be used to bind a bioactive agent to the modified saccharide, depending on the structure of the bioactive agent.

Again, according to the MPEP at 2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." Moreover, Applicant does not need to demonstrate therapeutic effects for particular diseases to enable the invention as claimed.

The present invention features glycoconjugates in which a bioactive agent is bound through a modified saccharide residue, e.g., UDP-GalNAc, to a compound which has an affinity for a target cell.

In the Examples, Applicants describe the rapid and sensitive detection of O-GlcNAc glycoslated proteins. As described by Applicants at page 48 of the specification, "the approach capitalizes on the substrate tolerance of GalT, which allows for chemoselective installation of an unnatural ketone functionality to O-GlcNAc modified proteins. The ketone moiety has been well-characterized in cellular systems as a neutral, yet versatile, chemical handle (Cornish et al., 1996; Mahal et al., 1997; Datta et al., 2002). Here, it serves as a unique marker to "tag" O-GlcNAc

glycosylated proteins with biotin. Once biotinylated, the glycoconjugates can be readily detected by chemiluminescence using streptavidin conjugated to horseradish peroxidase (HRP)." (line 14 – 21).

Applicants demonstrate in the Examples the ability of GalT to label the peptide TAPTS(O-GlcNAc)TIAPG, which encompasses an O-GlcNAc modification site within the protein CREB. Applicants use wild-type GalT and show that only partial transfer of the keto-sugar was observed by LC-MS, however when the Y289L mutant was used there was greater activity and complete conversion. (see page 40, line 14 – 22). Further, Applicants show that the same strategy can be used for the labeling of the O-GlcNAc glycosylated protein CREB (see, e.g. page 45, line 8 – 23).

As described in the specification at page 10, line 15, "the targeting compound (T)…is covalently bonded to a saccharide residue (S) with the use of a galactosyltranserfase enzyme, preferably beta-1,4-galactosyltransferase (GalT). In one embodiment of the invention, a modified saccharide (S) is covalently associated with the targeting compound with the use of a genetically engineered GalT, such as Y289L GalT (as discussed above). **The targeting compound can be any naturally occurring glycoprotein, glycolipid or carbohydrate or can be engineered, through chemical or recombinant techniques**. For example, if the targeting compound does not include a GlcNAc residue, the compound can be engineered, either through recombinant or chemical techniques known in the art, so as to include such a residue. Preferably, the targeting compound includes an N-acetylglucosamine (GlcNAc) residue."

Moreover, **binding specificity of glycoprotein, glycolipid or carbohydrate targeting compounds was known in the art at the time of filing**. For example, antibodies were known in the art at the time of filing to be targeting compounds. In particular, monoclonal antibodies against tumor antigens were known in the art as cancer therapeutic agents at the time of filing. For example, clinical trials were conducted with various monoclonal antibody therapeutics, such as bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody that has been evaluated in Phase II and Phase II trials, and Ramaswamy et al. (Clin Breast Cancer. 2003 Oct;4(4):292-4, provided herein) describe in combination with doclataxel in women with advanced breast cancer. Vande Putte et al. (Ann Rheum Dis. 2003 Dec;62(12):1168-77, provided herein), evaluate the efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in

DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Carbohydrate based targeted therapeutics were also well known in the art. For example, insulin is a well known therapeutic. Poulsen et al. (Diabetes Care. 2003 Dec;26(12):3273-9, provided herein), test a combination therapy with insulin as part, rosiglitazone, and metformin to treat reduced insulin secretion and insulin resistance in skeletal muscle and liver in type 2 diabetes. Further, the anticancer compound doxorubicin was well known by one of skill in the art at the time of filing as a targeted anticancer compound. Numerous publications from the time of filing teach the use of doxorubicin in clinical trials (see, e.g. Anton et al., Clin Breast Cancer. 2003 Oct;4(4):286-91, provided herein).

Accordingly, these antibodies that have been described in the art have one N-linked bi-antennary oligosaccharide attached at the IgG-Fc region. The terminal sugars of the oligosaccharide moiety come in several glycoforms: for example, some are desialated, degalactosylated, with only terminal N-acetylglucosaminyl residues. The monoclonal antibodies carrying only terminal N-acetylglucosamine on the bi-antennary oligosaccharide moieties, the G_0 glycoform, can be generated by de-sialylation and de-galactosylation of the monoclonal antibodies. With the mutant Tyr289Leu-Gal-T1 and UDP-α-galactose-that is C2-modified, a galactose moiety, that has a chemically reactive group attached at the C2 position of galactose, can then be transferred to G_0 glycoform of the monoclonal antibody. In the Tyr289Leu-Gal-T1 described in the present invention, the binding pocket for UDP-α-galactose has been enlarged to accommodate modifications at C2 position of galactose, for example the ketone moiety, that can serve as a neutral, yet versatile chemical handle. To these monoclonal antibodies (or any other glycoprotein, glycolipid or carbohydrate targeting compound), that carry the modified galactose with the reactive functional group, it is possible to couple any other agent.

The specification defines the term "bioactive agent" at p. 5, where "bioactive agent"

> means any chemical or biological material or compound suitable for delivery that induces a desired effect in or on an organism, such as a biological or pharmacological effect, which may include, but is not limited to, (1) having a prophylactic effect on the organism and preventing an

> undesired biological effect such as preventing an infection, (2) alleviating a condition caused by a disease or disorder, for example, alleviating pain or inflammation caused as a result of the disease or disorder, and/or (3) either alleviating, reducing, or completely eliminating the disease or disorder from the organism. As used herein, "bioactive agent" also refers to a substance which may be used in connection with an application that is therapeutic or diagnostic in nature, such as in methods for diagnosing the presence or absence of a disease or disorder in a patient and/or in methods for the treatment or prevention of a disease or disorder in a patient. As used herein, "bioactive agent" refers also to substances which are capable of exerting a biological effect in vitro and/or in vivo. Examples of suitable bioactive agents include diagnostic agents, pharmaceuticals, drugs, synthetic organic molecules, proteins, peptides, vitamins, steroids and genetic material, including nucleosides, nucleotides and polynucleotides.

Beginning on page 12, the specification teaches a wide variety of bioactive agents that are known in the art as useful in therapeutic or diagnostic methods or in medical therapies. At page 24, the specification teaches therapeutic uses.

Further, **it was known in the art at the time of filing that bioactive agents, such as those claimed, could be used to treat various diseases**. For example, the Campbell et al. reference (Cancer Res September 1, 2006 66; 8707), provided herein, demonstrates that statins prevent breast cancer growth in vivo and in vitro. The Cascone et al. reference (Ann Oncol. 2006 Mar;17 Suppl 2:ii46-48), provided herein, summarizes the clinical evidence on the anticancer activity of small molecule EGFR inhibitors in small cell lung cancer. Restivo et al. (Diabetes Care. 2006 Dec;29(12):2650-3), provided herein, teach botulinum toxin treatment for oropharyngeal dysphagia associated with diabetic neuropathy. Brennan et al. (N Engl J Med. 2006 Nov 9;355(19):1967-77), abstract provided herein, compare a rabbit antithymocyte polyclonal antibody or basiliximab, an interleukin-2 receptor monoclonal antibody, in renal transplantation graft rejection. Villa et al. (Br J Cancer. 2006 Dec 4;95(11):1459-66. Epub 2006 Nov 21), provided herein, show that a prophylactic

quadrivalent HPV vaccine was effective through 5 years for prevention of persistent infection and disease caused by HPV 6/11/16/18.

Clearly, the art supports the various known bioactive agents, as claimed and taught in the specification, were known such that any person skilled in the art could make and use the invention commensurate with the scope of the claims.

Although demonstration of specific therapeutic effects for particular diseases to enable the invention as claimed **is not necessary**, Applicants have particularly exemplified that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 – 1236 (provided herein). Applicants describe the utility of Y289L GalT to transfer a sugar residue with C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can be used for detection and targeting therapies. (see, p.1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided herein), Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation. Applicants accordingly request that the rejection be reconsidered and withdrawn.

Written Description

Claims 1 – 3, 43 – 45 and 49 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. (Office Action, p.10 - 11). Applicants respectfully disagree.

The Examiner argues that "claims 1 and 45 are broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound for use in any medical therapy." (Office Action, p.11).

The Examiner argues that "claim 2 is broadly drawn to any targeted glycoconjugate comprising any bioactive agent such as any and all polypeptide, any and all releasing factor, any and all releasing factor inhibitor, any and all carbohydrate, any and all nucleic acid and any and any targeting compound wherein the bioactive agent and the targeting compound are joined by any modified saccharide compound wherein the modified saccharide compound comprises galactose and any reactive functional group attached to the C2 position of the galactose ring for use in any medical therapy." (Office Action, p.11).

The Examiner argues that "claim 3 is broadly drawn to any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound such as any glycoprotein, any glycolipids, or any carbohydrate wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring. (Office Action, p.10).

The Examiner argues that "claim 43 is broadly drawn to a pharmaceutical composition comprising any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and a pharmaceutical acceptable carrier as a pharmaceutical composition for use in medical therapy of any and all diseases." (Office Action, p.12).

The Examiner argues that "claim 44 is broadly drawn to a kit comprising any targeted glycoconjugate comprising any bioactive agent and any targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of the galactose ring and a pharmaceutically acceptable carrier." (Office Action, p.12).

In the interest of compact prosecution, the above rejections will be addressed together. The Examiner argues that "the scope of each genus includes many members with widely differing structural, chemical, and physiochemical properties of targeting compound and bioactive agent such as widely differing amino acid sequences, nucleotide sequences and biological functions in the claimed glycoconjugate...(and) each genus is highly variable because a significant number of structural and biological differences between genus members exist." (Office Action, p.12).

The present claims are directed to a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

As discussed above, targeting compounds are described in the specification at page 10 and page 18. Applicants provide a particular example of a antibodies as a targeting compound at p. 20 of the specification. Further, targeting compounds were well known in the art as described above.

As discussed above, bioactive agents are described beginning at page 10 - 18. Further, bioactive agents were well known in the art as described above.

Applicants submit that the claims are sufficiently described in the specification to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully request that the foregoing rejections be withdrawn.

35 U.S.C. §102

Claims 1 – 3 and 45 were rejected under 35 U.S.C. §102(a) as being anticipated by Vocadlo et al. (PNAS USA 100(16):9116 – 9121, August 5, 2003). Applicants respectfully traverse this rejection.

Claims 1 – 3 and 45 were rejected under 35 U.S.C. §102(e) as being anticipated by US Patent No. 7,332,355 (filed 11/17/2004 claiming priority to provisional application No. 60/523,523, filed on 11/18/2003). Applicants respectfully traverse this rejection.

In response to the above rejections, Applicants submit herein a Declaration under 35 CFR 1.31 to establish invention of the targeted glycoconjugates, as claimed, prior to the effective date of the Vocadlo and 7,332,355 references.

Applicants respectfully request that the foregoing rejection be withdrawn.

35 U.S.C. §103(a)

Claims 1 – 3, 43 – 45 and 49 were rejected under 35 U.S.C. §103(a) over US Patent No. 7,265,085 (the '085 reference herein) and in view of US Patent 7,332,355 (the '355 patent, cited above), Ramakrishnan et al. (J Biol Chem 277 (23):20833 – 20839, June 2002) and Hang et al. (J Am Chem 123: 1242 – 1243, 2001). (Office Action, p.20). Applicants respectfully traverse the rejection.

The claims have been set forth above.

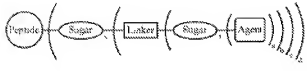
The Examiner argues that "(t)he '085 reference teaches various targeted glycoprotein such as transferring-SA linker-GDNF wherein the reference targeting compound such as transferrin and bioactive agent such as GDNF are joined by a modified saccharide compound such as o-Glc-NAc modified galactose using beta-1,4 galactosyl transferase." (Office Action, p.20).

The '085 reference is directed to methods of remodeling a peptide to attach a specific glycan structure. The '085 reference teaches that at least one of the glycosyl donors comprises a modifying group (and) preferably, the modifying group is a member selected from the group consisting of a polymer, a therapeutic moiety, a detectable label, a reactive linker group, a targeting moiety and a

peptide. That is, the '085 reference teaches that the glycans structures are remodeled in order to be useful (see col. 63 – 65). Conjugates of the invention are described beginning at col. 66:

> In a first aspect, the present invention provides a conjugate between a peptide and a selected moiety. **The link between the peptide and the selected moiety includes an intact glycosyl linking group interposed between the peptide and the selected moiety**. As discussed herein, the selected moiety is essentially any species that can be attached to a saccharide unit, resulting in a "modified sugar" that is recognized by an appropriate transferase enzyme, which appends the modified sugar onto the peptide. (col. 66 – 67, emphasis added.

Typical conjugates of the invention are shown by the structure at col. 67, line 5, where "symbols a, b, c, d and s represent a positive, non-zero integer; and t is either 0 or a positive integer. The 'agent' is a therapeutic agent, a bioactive agent, a detectable label, water-soluble moiety or the like…(and) (t)he linker can be any of a wide array of linking groups, infra…(or) a single bond or a "zero order linker."



The '085 reference exemplifies such a conjugate at col. 68, line 6, where "EPO is conjugated to transferrin…(or) EPO is conjugated to glial derived neurotropic growth factor (GDNF). In these embodiments, each conjugation is accomplished via **a bifunctional linker that includes an intact glycosyl linking group at each terminus of the PEG moiety**, as aforementioned." (emphasis added).

Clearly, the glycoconjugates that are taught by the '085 reference are different from the present claims, where the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), where the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. The structure of these conjugates is different from the present invention as claimed.

The Examiner argues further that "the invention differs from the teachings of the reference only in that the glycoconjugate wherein the modified UDP galactose acetyl group (UDP-GalNAc) comprises a ketone group attached to the C2 position of galactose ring." (Office Action, p.21).

None of the '355, Ramakrishnan or Hang references cure the defects of the '085 reference.

The Examiner argues that "(t)he '355 patent teaches a method of making glycoconjugate comprising a bioactive agent such as antibody binding probe...and a targeting compound such as CREB protein or α-crystallin or peptide...joined by a modified UDP galactose acetyl group comprising a ketone attached to the C2 position of the galactose ring for diagnostic method." (Office Action, p.21).

The Examiner argues that "Ramakrishnan et al. teach a modified beta-1,4 galactosyltransferase having a tyrosine at position 289 substitute for Lysine that enhances the GalNAc-transferase activity equal to that of Gal-T activity." (Office Action, p.15).

The Examiner argues that "Hang et al. teach the use of unnatural or modified monosaccharide such as 2-ketosugars or 2-keto isotere of GalNAc sugar or 2-acetaminodsugars as the substrate for GalNAc transferase for metabolic glycoprotein engineering in CHO cells. Hang et al. further teach the ketone reactive group produced by 2-ketosugars can be used as a molecular handle and more accessible for chemical reaction with biotin hydrazide." (Office Action, p.15).

As discussed above, the '355 reference is not a proper reference.

The Ramakrishnan and Hang references do not make up for the defects of the '085 reference.

The '085 reference does not teach a targeted glycoconjugate comprising a bioactive agent and targeting compound that are joined by a modified UDP galactose acetyl group (UDP-GalNAc). Nor does the '085 reference provide teaching or suggestion to modify any position of the saccharide ring preferably over any other position. It would not have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the beta-1,4 galactosyl transferase that catalyse the transfer of galactose in the target conjugate of the '085 patent for the modified beta-1,4 galactosyltransferase taught by the Ramakrishnan reference using any modified monosaccharide such as 2-ketosugars or 2-ketoisostere of GalNAc as a molecular handle as taught by the Hang reference.

In view thereof, reconsideration and withdrawal of the rejection are requested.

CONCLUSION

For the reasons provided, Applicant submits that all claims are allowable as written and respectfully requests early favorable action by the Examiner.

If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney of record.

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